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Working Memory and Response Inhibition in Patients With Bipolar I Disorder During Euthymic Period

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Background: Several cognitive domains, including attention, memory, and executive functions are impaired in bipolar disorder.
Objectives: This study aimed to investigate two executive functions (working memory and response inhibition) in patients with bipolar I disorder during remission of the symptoms.
Patients and Methods: In this case-control design, 30 bipolar I patients (18 to 45 years old) were matched with 30 ones in the control group in terms of age, gender, and education. The patients were selected from Roozbeh Psychiatric Hospital (a hospital affiliated to Tehran University of Medical Sciences) from May to October 2013. They were evaluated and contrasted using working memory (Spatial Span and Spatial Working Memory (SSP and SWM)) and response inhibition (Stop Signal Task (SST)) tests.
Results: We used independent t-tests for comparing and contrasting 2 groups on total and sub-scales scores of these 3 tests. In terms of SWM test there was a significant difference in between-group error between the two groups (P = 0.05); there was also a meaningful difference between the strategies used by two groups (P = 0.05). In SSP test, a significant difference appeared between averages of span length of the two groups. In the first and last item delays, there was also a clear difference, but the total error index was not noticeably different. In SST test, the direction error indicator in start-stop trials indicated a major difference, while in successful stops ratio, the case group had a lower ratio. In addition, reaction time to stop signs in bipolar group was meaningfully lower than the control group.
Conclusion: In conclusion, even during remission phase, executive dysfunction is detectable at least in some areas in patients with bipolar disorder.

Keywords: Bipolar Disorder; Executive Functions; Inhibition; Working Memory

1. Background

Bipolar disorder is characterized by fluctuation and relapses of mania and depression periods. This pathologic mood definitely impacts on cognitive functions. Several cognitive domains, including attention, memory, and executive functions are impaired in bipolar disorder (1, 2). Meanwhile, in recent decades, there has been an increasing tendency to study neurocognitive deficits like executive functions among researches (3). Executive functions are a series of problem-solving tasks to achieve specific goals (4), including abilities like attention, reasoning, planning, working memory, response inhibition, and interfering factors' control. These functions are vital for human complex behavior. Disruption in these functions of often ten causes psychiatric or behavioral disorders, suggesting their important role in human complex behavior (5). Executive functions are hypothesized in explanation of many disorders such as schizophrenia (6), obsessive-compulsive disorder (7), autistic disorder (8), eating disorders (9), panic disorder (10), and post-traumatic stress disorder (11). Bipolar disorder is among these disorders (12).

In fact, quite enough studies have repeatedly shown that bipolar patients suffer from cognitive impairments both during acute phases (13) and remission/euthymic periods (14, 15). Meta-analysis of Robinson et al. (12) on 26 studies (689 patients and 721 controls), suggested that aspects of executive function had a large effect size ([$d \geq 0.8$] indicating marked impairment), whereas other cognitive domains, including response inhibition and set shifting had medium effect ($0.5 \leq d \leq 0.8$), and finally verbal fluency, immediate memory, and sustained attention had small effect sizes ($0.2 \leq d \leq 0.5$). An updated meta-analysis of Robinson et al. (12), which added studies on first-degree relatives provided the same results on

cognitive impairments for euthymic patients and to lesser degrees, but still significantly different from healthy controls, for first-degree relatives (16).

Because cognitive impairment appears to occur in the early stages of bipolar disorder and increases both during depressive episodes and after periods of mania, some researches consider this defect as a state marker (17, 18). Other studies have shown that cognitive deficits exist both after a long symptom-free and controlled subthreshold symptoms (12). A recent research with a considerable follow-up period has also spotted that cognitive deficits are stable features in bipolar patients with normal mood during the next 6 years (19).

Among cognitive deficits in bipolar disorder, response inhibition impairment accompanies manic symptoms (e.g. impulsivity, psychomotor agitation, over-talkativeness, overspending, and risky sexual behavior). Some researchers suggest that impulsivity, which includes some defects in response inhibition, is higher in patients with bipolar disorder even during normal mood periods (20, 21).

The importance of cognitive deficits in euthymic patients has many aspects. Cognitive impairments have adverse impacts on functions such as daily activities, job, interpersonal relationships, and quality of life (22); also they have significant correlation with weak psychosocial functioning in the future (19). On the other hand, due to negative psychosocial consequences of cognitive deficits on both patients' medication compliance (13) and psychological interventions complementing pharmaceutical treatment (23), identification and rehabilitation of these defects stress their particular importance. In other words, empowerment of bipolar patients, in terms of psychosocial aspects, has been a major concern for clinicians.

Studies like this can provide mental health practitioners with useful intervention strategies, because investigators soon found that effectiveness of psychosocial interventions in these patients is bound to considering their cognitive limitations (24). As a new approach in last few years, it aims to help these patients by intervening on their basic cognitive components, called neuropsychological remediation or cognitive rehabilitation (25). By manipulation of basic cognitive processes, these interventions are supposed to improve cognitive functions and consequently promote psychosocial functioning of bipolar patients (26).

It seems that despite convincing evidence on cognitive impairments during euthymic periods, more researches are still needed with methodologically solid designs to control confounding factors such as medication, and subsymptoms effects (12); and applying measures with high sensitivity and specificity for evaluating cognitive elements of bipolar patients (16); as well as using a well-designed battery for assessing cognitive impairments (27).

2. Objectives

This study aimed to evaluate two executive functions (working memory and response inhibition) in euthymic bipolar patients and comparing them to the control group. Our hypothesis is that working memory and response inhibition in euthymic patients are weaker compared to healthy controls.

3. Patients and Methods

In this case-control study, 30 patients (18 to 45 years) with bipolar diagnosis admitted to Roozbeh Psychiatric Hospital (from May to October 2013) entered the study and were compared to 30 healthy controls. In patients group, 25 were manic in which 17 ones had psychotic features; the other 5 patients had mixed episodes. The patients were examined within 3 to 4 weeks after symptoms remission (in euthymic period). After psychiatric evaluation and determining their diagnosis, and obtaining their primary consent, the patients were referred to a researcher. Then the researcher described the study to them and if they wanted to participate in the study, they would be asked to complete a consent form. After that, they were interviewed using Structured Clinical Interview for DSM-IV for Axis (SCID-I) disorders. The interviews were carried out by a clinical psychologist.

Inclusion criteria included age between 18-45 years, diagnosis of bipolar disorder based on psychiatrist diagnosis, and SCID-I diagnoses. Exclusion criteria consisted of any obvious cognitive disorders, major depressive episode, clinical anxiety, substance abuse, and mental retardation. Most of the patients were polymedicated. All 30 patients were receiving mood stabilizers; 22 of them were taking anxiolytics; and 17 took also anti-psychotic. None of the patients were getting electro convulsive therapy.

In addition, the control group was interviewed using SCID-I as a diagnostic tool for ruling out psychiatric disorders; and if they met the criteria for any axis I disorders or a history of these disorders, they were excluded. The control group subjects were selected among hospital staff and other available healthy people. They were assessed based on inclusion and exclusion criteria. Participants also matched with the patient group based on age, gender, and degree of education.

3.1. Measures

To assess executive functions (working memory and response inhibition), Cambridge Neuropsychological Test Automated Battery (CANTAB) was applied, which was originally developed at Cambridge University in 1980s (28) and now provided by Cambridge Cognition (www.cambridgecognition.com). It is a computer-based cognitive assessment system consisting of 22 neuropsychological tests for various cognitive functions. These tests are administered to subjects using a touch screen computer with no specific language or culture bound, it is based on the standard cognitive tests that are routinely used in psychological assessment (29). Since the tests have no use in diagnosis or determining disorder and are based on comparison with no need to the mean score like other

neuropsychological tests, they can be applied without confirming their reliability and validity to reflect between-group differences. These test kits are validated in a sample of 3000 people. In this study, to assess working memory, SWM, SSP, were used and response inhibition was obtained through SST test.

3.2. Spatial Working Memory

This test is a form of self-ordered searching task. It assesses the ability to retain spatial information and manipulate remembered items in working memory, while the subject performs the task to achieve goals. The test consists of a series of colored squares (boxes) that are displayed on the screen. According to the guidelines, by touching boxes and using a process of elimination, the subject should find one hidden blue 'token' in each of boxes and use them to fill up an empty column on the right hand side of the screen. Each box has only one hidden blue sign. When it is found, the box no longer provides another sign. Thus it seems that in the next item, searches should be limited to boxes that contain blue signs. This process goes on until all blue signs of the boxes are discovered on the screen. When the trial ends up, a new one begins (with new color and position different from previous trials). This test consists of 4 experimental trials and every trial has 3 boxes for search (the first 4 trials will not be scored), then test continues with 4, 6, and 8 boxes. The variables used in SWM test include errors (between-group, within-group, and double errors), strategy, and latency (time from when the task is presented until the participant's first touch for opening the box) (27).

In this test, when a subject touches a box that blue signs have already been found in, errors (between-group) are recorded. Within-group errors include the number of errors occurring within a search, for example, the frequency of selecting a box that had been found empty in previous searches, (frequency of re-selection the empty box in a trial). Double errors are calculated when the participant makes an error (re-selection of an empty box) that can simultaneously fall within group error categories. Owen et al. (30) have proposed an effective strategy for accomplishing this task. To start, a predetermined sequence of boxes marked with a blue sign were found to start and when it comes back, the new scouring is to begin. Estimated use of this strategy (strategic points) is obtained from the total number of times that participants seek a new one with 6 and 8 boxes. The high score indicates a poor use of these strategies and a low score indicates an efficient use.

3.3. Spatial Span

Spatial span assesses working memory capacity, which is a visuospatial analogue of the digit span test. This test measures the ability to remember the location and order of a set of visual stimuli (white squares) displayed on the screen. The number of boxes is increased from 2 at the start of the test to 9 at the end, and sequence and color are changing through the test. Each stage includes 3 tentative efforts. The test is stopped when the participant fails in all 3 trials of a stage. Time span is defined as the highest level that the subject can remember in a trial. This measurement requires both visual and spatial components representing the ability to store data temporarily or online in order to plan more operations in the future. This test has 5 variables span length, mean time to first response (span length 2), mean time to last response (span length 2), total errors, and total usage errors (30, 31).

3.4. Stop Signal Task

This test measures the response inhibition ability. In each experimental trial, the participant should press the arrow that displayed on the screen (according to the arrow's left or right direction, the subject should press the corresponding button). If an auditory tone is presented, the participant must inhibit that response. This test consists of two sections: In the first one, the participant is introduced to press the left hand button when he sees a left-pointing arrow, and right hand button when seeing a right-pointing arrow. There is one block of 16 trials for the subject to practice this. In the second section, the participant is told to continue pressing buttons when they see the arrows, as before, but, if they hear an auditory signal (a beep), they should withhold their response and not press the button. This part consists of 4 blocks each containing 16 trials (total trials: 64). The variables of SST include 5 items including direction errors on stop and go trials, proportion of successful stops, median correct reaction time on go trials, stop signal delay, and stop signal RT (31).

3.5. Young Mania Rating Scale

This scale was developed by Young, Biggs, Ziegler, and Meyer (32) for mania evaluation. This measure rates symptoms of bipolar disorder in mania episode and consists of 9 items. The scoring scale is based on severity of symptoms (total score: 60). There was a high correlation between scores of two independent clinicians on both the total score (0.93) and the individual item scores (0.66 to 0.92) (32). Reliability and validity of this scale were acceptable in an Iranian sample (Isfahan province) (33). In this study, concordant validity of YMRS with the World Health Organization World Mental Health Composite International Diagnostic Interview (WHO WMH-CIDI) was 0.87. Discriminatory analysis results indicated 17.14 and the optimal cut-off point with 98.4% sensitivity and 98.4% specificity. YMRS (Young Mania Rating Scale) is a valid instrument with acceptable sensitivity and specificity which can be applied in both clinical and research settings.

3.6. Beck Depression Inventory-II

This scale was first applied by Beck in 1961 and then revised in 1971. It is a 21 multiple-choice test with 0 to 3

scored items. Its test-retest reliability has been reported between 0.48 to 0.86 and a mean of 0.86 (34). Internal consistency of BDI-II was estimated to be 0.73-0.93 and the correlation between parallel forms was 0.89. Concurrent validity of the questionnaire with the Hamilton Rating Scale for Depression (HRSD) and depression subscale of SCL-90 has been 0.71 and 0.89, respectively (34). In a study by Ghassemzadeh et al. (35) on a Persian version of BDI-II, the test had high internal consistency (Cronbach α = 0.87) and acceptable test-retest reliability (r = 0.74).

3.7. Beck Anxiety Inventory

This questionnaire consists of 21 multiple choice items (scoring from 0 to 3), which assesses the severity of anxiety. The total score ranges from 0 to 63. This questionnaire focuses mainly on physiological aspects of the anxiety. Three items relate to anxious mood, 3 ones assess specific phobias and other questions evaluate autonomous hyperactivity symptoms and tension. Beck et al. (36) have reported the internal consistency of this scale as 0.93 and its test-retest reliability as 0.75. This questionnaire was validated in Iran by Kaviani and Mousavi (37). In their study, internal consistency measured by Cronbach α was 0.92; test-retest reliability was 0.83 and within class validity was 0.83.

SPSS-19 was used to analyze the data. Independent t-test was applied to assess differences between means considering $P < 0.05$ significant level. Descriptive statistics were applied for the demographic variables.

4. Results

In this study, 30 patients (15 females, 15 males) and 30 healthy controls (15 females, 15 males), were evaluated. The two groups were matched up to age (mean ± SD of patients, 32.6 ±7.85 years; the control group 32.43 ± 7.64 years) and had no significant differences. There were no significant differences between the two groups in terms of degree of education ($P < 0.05$, df = 58, t = -0.294) (number of patients in primary-secondary school level were 7 (23.3%), and in control group was 5 (16.7%); in the second category, high school/diploma level, there were 12 patients (40%), and 15 controls (50%); in diploma/BA level, 9 patients (30%), and 7 controls (23.3%), and in the last category, postgraduates (MA and Ph.D.), there were 2 people (6.7%) for patients group, and 3 ones for control group (10%)). Participants' scores regarding BAI were not significantly different ($P < 0.05$, df = 58, t = -0.202). There were also no significant differences in BDI-II scores ($P > 0.05$, df = 58, t = 2.84), and the mean score on YMRS was 7 in patients groups.

Table 1 presents the results of the SST test. Regarding direct errors on stop and go trails, bipolar group scored significantly higher than controls ($P < 0.05$, t = 3.08) and the proportion of successful stops in the bipolar group was significantly lower than the control group ($P < 0.05$, t = -2.02). Stop signal reaction time in bipolar group was significantly greater than the control group ($P < 0.05$, t = 4.14). Median correct reaction time on go trails was not significant between the two groups ($P < 0.05$, t = 1.16). The delay between the two groups was not significant on stop signal delay ($P < 0.05$, t = -1.13).

Table 2 presents SSP results. With regard to span length, bipolar group got lower scores than the non-clinical group, and this difference was significant ($P < 0.05$, t = -3.89). The mean latency to first response in the bipolar group was higher than the control group, and the difference was significant ($P < 0.05$, t = 3.40) and the mean response latency in the last item was also significantly greater in bipolar group ($P < 0.05$, t = 3.88). As shown in Table 2, the mean of total errors in bipolar group is higher than the control group, but this difference was not significant ($P > 0.05$, t = -1.14) and the total usage errors was similar between the two groups ($P < 0.05$, t = 0.291).

Table 1. Comparison of Patients and Control Group in Response Inhibition variables

Variables	Mean ± SD	df	T	P Value
Direct errors on stop and go trails		58	3.08	0.003 [a]
Patient, n = 30	9.23 ± 15.54			
Control, n = 30	0.4667 ± 0.7760			
Proportion of successful stop		58	-2.02	0.048 [a]
Patient, n = 30	0.5093 ± 0.1559			
Control, n = 30	0.6097 ± 0.2223			
Median correct reaction time on go trails		57	1.16	0.247
Patient, n = 30	914.95 ± 287.59			
Control, n = 29	823.67 ± 311.88			
Stop signal delay		57	-1.13	0.259
Patient, n = 30	546.72 ± 163.25			
Control, n = 29	607.01 ± 237.61			
Stop signal reaction time		57	0.14	0.001 [a]
Patient, n = 30	368.22 ± 163.65			
Control, n = 29	216.65 ± 111.75			

[a] $P < 0.05$.

Table 3 shows the test results of SWM. The total number of between-errors was significantly higher in bipolar group ($P < 0.05$, $t = 3.98$). Between-group errors in 4, 6, and 8 boxes stages were significantly higher in bipolar group compared to the control group ($P < 0.05$, $t = 2.25$; $P < 0.05$, $t = 3.30$; and $P < 0.05$, $t = 3.76$, respectively). Strategies used in clinical and non-clinical groups were significantly different ($P < 0.05$, $t = 2.33$). The total error was greater in bipolar group compared to the control group ($P < 0.05$, $t = 3.76$). In 4 boxes step, there was no significant difference in total errors between the two groups ($P > 0.05$, $t = 1.91$), but total errors in 6 and 8 boxes levels were higher in bipolar group compared to the control group ($P < 0.05$, $t = 3.24$; $P < 0.05$, $t = 3.06$, respectively). In double-error and within-group error variables the two groups were not significantly different.

Table 2. Comparison of Patients and Control Group in Working Memory variables

Variables	Mean ± SD	df	T	P Vaue
Span length		58	-3.89	0.001 [a]
Patient, n = 30	4.90 ± 1.09			
Control, n = 30	6.03 ± 1.15			
Mean time to first response		58	3.40	0.01 [a]
Patient, n = 30	3606.25 ± 924.58			
Control, n = 30	2992.36 ± 349.35			
Mean time to last response		58	3.88	0.001 [a]
Patient, n = 30	4617.68 ± 1070.75			
Control, n = 30	3810.53 ± 380.74			
Total errors		58	-1.14	0.256
Patient, n = 30	12.47 ± 4.32			
Control	14.07 ± 6.30			
Total usage errors		58	0.291	0.772
Patient, n = 30	2.10 ± 1.42			
Control, n = 30	2 ± 1.23			

[a] $P < 0.05$.

Table 3 . Comparison of Patients and Control Group in Working Memory Variables

Variables	Mean ± SD	df	T	P Value
Between errors		58	3.98	0.001 [a]
Patient, n = 30	53.37 ± 22.32			
Control, n = 30	33.13 ± 16.64			
Between errors 4 boxes		58	2.25	0.028 [a]
Patient, n = 30	2.37 ± 2.91			
Control, n = 30	1 ± 1.57			
Between errors 6 boxes		58	3.30	0.002 [a]
Patient, n = 30	17.27 ± 11.22			
Control, n = 30	9.57 ± 6.07			
Between errors 8 boxes		58	3.42	0.001 [a]
patient, n = 30	33.73 ± 13.25			
Control	22.57 ± 11.97			
Strategy		58	2.33	0.023[a]
Patient, n = 30	38.80 ± 4.74			
Control	36.33 ± 3.33			
Total errors		58	3.76	0.001 [a]
Patient	56.30 ± 23.49			
Control	35.97 ± 18.01			
Total errors 4 boxes		58	1.91	0.06
Patient, n = 30	3.13 ± 3.84			
Control, n = 30	1.53 ± 2.46			
Total errors 6 boxes		58	3.24	0.002 [a]
Patient, n = 30	18.20 ± 11.82			
Control, n = 30	10.20 ± 6.50			
Total errors 8 boxes		58	3.06	0.003 [a]
Patient, n = 30	34.97 ± 13.93			
Control, n = 30	24.23 ± 13.16			

[a] $P < 0.05$.

5. Discussion

In this study, the performance of working memory and response inhibition of bipolar patients were assessed during remission phase of mania symptoms. SST results showed that the direction errors in start-stop trials were higher in bipolar group; and in successful stop ratio, the patients were less successful than the controls. In addition, the stop reaction time of bipolar group was greater than the control group, indicating that people with bipolar disorder have more errors in SST even after remission of acute mania symptoms. The results also showed that the time between moving and stopping, considered as response inhibition reaction time (SSRT), was higher in patients than controls. In fact, it took more time for bipolar patients to inhibit their responses. These results are consistent with the findings of a meta-analysis study done by Hajek (38). This meta-analysis included 30 studies, consisting of 635 patients and 677 controls. Findings of this study showed that the patients' performance during periods of normal mood (228 patients and 277 controls) was different from healthy controls, also the accuracy level in bipolar group in doing GNG test, SSRT, and Stroop attention test was weaker than control group during periods of normal mood. There were similar deficiencies in not paying attention to Stroop interferes, and stop signal reaction time (SSRT) was significantly different from matched control group. The patient group had a lower precision and needed more time to inhibit responses. In this study, the involved brain areas were also examined by the functional magnetic resonance imaging (FMRI). Furthermore, the study of Gruber (39) compared 30 patients suffering from major depression, 17 patients with manic bipolar disorder, and 22 patients with depressive bipolar disorder by several neurocognitive tests (memory, attention, executive function, and SST). Evaluations were done at admission and 7 weeks after discharge (in recovery period). In the first evaluation, manic patients had lower performance in response inhibition reaction time (SST) compared to depressive bipolar patients (EF = 0.75). Although all three groups showed significant improvement after the follow-up period, deficiency in some domains (especially executive function) remained constant. Manic patients reported most errors among the three groups. In addition patients with mania had weaker results in inhibition of start responses than patients with major depression (EF = 0.87) and also had poorer performance compared to depressed bipolar patients (EF = 0.58). They also had slower reaction time than patients with bipolar depression at the start of the responses (EF = 0.55). Larson et al. (40) had findings similar to the present study. In their study, two groups of bipolar patients (15 ones during manic episode, and 18 patients during normal mood period), were compared to 18 healthy controls using Object Alternation Task. Patients during both periods of mania and normal mood showed greater errors in response inhibition compared to the control group. Other researches (41, 42) have confirmed deficits in response inhibition during periods of normal mood in patients with bipolar disorder. There are few studies inconsistent with previous ones (43). In this study, 20 patients with bipolar disorder during period of normal mood were compared to 20 controls in response inhibition test (GNG); they were also examined by FMRI during this test. Results showed that performance was similar in both groups, while the activity pattern of involved brain areas in response inhibition was different.

On the other hand, both the meta-analysis studies by Robinson et al. (12) that examined the patients during periods of normal mood and Bora (44) that examined the close relatives of bipolar patients, suggested that response inhibition was the most prominent factor in the phenotype of bipolar disorder. This finding is supported by other researches; patients who are at risk of bipolar disorder show structural changes in areas associated with inhibition (38). In conclusion, it seems that enough evidence supports the idea that response inhibition deficit is an independent phenomenon existing beyond pathological mood episodes in patients with bipolar disorder.

The results of the second hypothesis, in SWM test, showed more within-group errors in bipolar patient. In the strategies employed index, there was also significant difference between the two groups, in other words, bipolar patients in normal mood period had more errors on SWM test. This finding regarding within-group error is consistent with Thompson et al. (45). In their research 63 bipolar patients during normal mood period (27.3 months on average) were compared to 63 healthy participants. Results showed that patients had more within-group errors compared to healthy group in SWM, but in strategies employed by the two groups there was not any significant difference, which contradicts with our finding regarding strategies. In addition, Sweeney et al. (46) using CANTAB, compared 58 patients with major depression, 21 bipolar patients in depressive phase, 14 ones in mania or mixed episodes, to 51 normal individuals. SWM test results showed no significant differences between groups. Patients in mania or mixed episodes had lower performance compared to depressed patients and healthy controls. Also, in the employed strategies, there were significant differences between groups; patients in manic or mixed phase had the least stability compared to those in the control group or depressed patients.

The third part of our findings regarding SSP test indicated that the span length of clinical group was significantly lower compared to the healthy group. In fact, the clinical group could remember fewer items. A significant difference existed in the meantime to first response and meantime to last response delays between the two groups, so that patients needed more time to do their first and last touches. These are consistent with the results of Sweeney et al. (46) that bipolar patients in normal mood period had

significantly weaker performance in SSP test compared to the control group. Our findings in this section are also compatible with the findings of Dittmann et al. (15), who examined 65 patients with bipolar disorder type I, 38 patients with bipolar disorder type II (both during the period of normal mood), and 38 healthy controls using a brief neuropsychological battery. Results indicated that bipolar patients had poorer performance in some items, such as working memory (measured by the Wechsler Memory Subscale) compared to the control group. There was no significant difference in cognitive functioning between the two groups. Finally, it was in agreement with other studies confirmed impaired cognitive functions during periods of normal mood in patients with bipolar disorder (23), such as Cavanagh's study (23), which assessed memory and verbal learning in patients with bipolar disorder in euthmic phase compared to normal group. Their results showed that patients demonstrated significantly poorer performance in immediate recall. In fact, they could retain fewer items. Findings also revealed negative correlation between frequency of mania episodes and memory function (delayed recognition domain).

Our study has some limitations that make it difficult to generalize these findings. First of all, our sample is small. It would be useful to replicate this study with a large sample. The second limitation is the possible interference of sub-symptoms in cognitive functioning of the patients and the third one is controlling the effect of medications. Most of our patients were on medications including mood stabilizers, antipsychotics, and anxiolytics. Early evidence relating positive effects of mood stabilizers on neurocognitive functioning of bipolar patients (47) and at the same time some negative effects of antipsychotics on neuropsychological functioning in bipolar patients (48, 49) make it hard to draw conclusion about medication effects. We suggest that further researches with longitudinal designs and using homogenous patients based on their medication regimes can shed light on some of these limitations. We also suggest that future studies should do more with these confounding factors. In conclusion, current research suggests that bipolar patients had some inabilities in working memory ability and need more time to inhibit their responses compared to the control group. These findings have some clinical implications for practitioners such as paying more attention to cognitive symptoms that seems to be impaired even during remission. Also they would be better to consider neuropsychological remediation in their bipolar patients' treatment protocols.

Future studies should answer other remaining questions such as what cognitive function in which type of bipolar disorder is stable or transient, and how much these stable cognitive dysfunctions take part in patients' specific psychosocial areas of functioning. Also they should clearly respond to questions regarding severity of the illness, and specific clinical features like presence of psychosis, substance abuse, and so on.

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Authors' Contributions

Zahra Farahmand did the project as the main reseacher and drafted the manuscript. Mehdi Tehrani-Doost designed and supervised the project and contributed to the analysis and interpreting the findings. He also read and approved the final manuscript. Homayoun Amini contributed to patient selection and revising the manuscript. Abolfazl Mohammadi contributed to analysis and revising the manuscript. Mosleh Mirzaei contributed mainly in drafting the manuscript, improving the writing and grammatical quality of the article. Azar Mohammadzadeh had a major role in data gathering and testing. All authors read and approved the final manuscript.

Declaration of interest

None Declared.

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